PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Shiro SHIBAYAMA et al

Appln. No.: **Continuation of 09/246,355** Group Art Unit: **1646**

Filed: **February 25, 2002** Examiner: **Mertz, P.**

For: A NOVEL POLYPEPTIDE AND DNAS ENCODING IT

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the above-identified application as follows:

IN THE TITLE:

Please replace the title with the following amended title:

A POLYPEPTIDE AND DNAs ENCODING IT

IN THE SPECIFICATION:

Please amend the specification by inserting the following sentence before the first line:

This is a continuation of Application No. 09/246,355 filed February 8, 1999, which is a continuation application of U.S. Application No. 08/852,811 filed May 7, 1997, which is a continuation application of U.S. Application No. 08/439,457 filed May 11, 1995; the above noted prior applications are all hereby incorporated by reference.

Please move the section of the specification entitled "Field of the Invention" (encompassing lines 1-6, page 1) to be inserted before the section entitled "Related Arts" at page 1.

Please replace the paragraph encompassing lines 9-17, page 1, with the following paragraph:

Related Art

Vascular organization consists of endothelial cells, smooth muscle cells and fibroblasts. Especially, endothelial cells have the following serious functions;

1) regulation of vasotonia,

2) regulation of antithrombus and

3) response to disturbance factors of inflammation or immunity. It is thought that disturbance of the endothelial cells or anomaly of functional modulation is one cause of arteriosclerosis or inflammatory diseases.

Please replace the paragraph encompassing lines 11-16, page 2, with the following paragraph:

Summary of the Invention

As described previously, it is clear that factors concerning regulation of vasotonia, response to disturbance factors of inflammation or immunity and regulation of antithrombus are produced from vascular endothelial cells. These facts suggest that the other factors which have the same functions are produced from endothelial cells.

Please replace the paragraph encompassing lines 17-19, page 2, with the following paragraph:

The present inventors have directed their attention to this point and energetic research has been carried out in order to find novel factors which an endothelial cell generates.

Please replace the paragraph encompassing lines 1-2, page 3, with the following paragraph:

factor, which makes it difficult to isolate and to purify the factor and to confirm its biological activity.

Please move the section of the specification entitled "Brief Description of the Drawings" (found at page 27), to be inserted after line 18, page 3.

Please replace the paragraph encompassing lines 19-24, page 3, with the following paragraph:

Detailed Description of the Invention

The present invention is related to:

(1) a polypeptide having an amino acid sequence shown in SEQ ID No. 1,

(2) a DNA encoding the polypeptide described above (1),

(3) a DNA having a nucleotide sequence shown in SEQ ID No. 2, and

(4) a DNA having a nucleotide sequence shown in SEQ ID No. 3.

Please replace the paragraph encompassing lines 1-9, page 4, with the following paragraph:

polypeptide of the present invention has a signal peptide region which is located from the methionine (Met) at the 1st position to the serine (Ser) at the 24th position in the amino acid sequence shown in SEQ ID NO. 1. The essential sequence for biological activity is the amino acid sequence where the signal peptide is removed from the amino acid sequence. The signal

peptide is not required for biological activity. On the other hand, the peptide of the present invention was confirmed transmembrane domain which is located from amino acid at the 119th position to amino acid at the 146th position in the amino acid sequence shown by SEQ ID No. 1 (see Figure 3).

Please replace the paragraph encompassing lines 13-20, page 5, with the following paragraph:

A further embodiment of the invention provides replication and expression vectors comprising DNA according to the invention. The vectors may be, for example, plasmid, virus or phage vectors provided with an origin of replication, optionally a promoter for the expression of the DNA and optionally a regulator of the promoter. The vector may contain one or more selectable marker genes, for example an anpicillin resistance gene. The vector may be used in vitro, for example of the production of RNA corresponding to the DNA, or used to transfect or transform a host cell.

Please replace the paragraph encompassing lines 3-7, page 6, with the following paragraph:

DNA according to the invention may also be inserted into the vectors described above in an antisense orientation in order to provide for the production of antisense RNA. Antisense RNA may also be produced by synthetic means. Such antisense RNA may be used in a method of controlling the levels of a polypeptide of the invention in a cell.

Please replace the paragraph encompassing lines 1-5, page 7, with the following paragraph:

As is well-known, there are one to six kinds of codon as that encoding one amino acid (for example, one kind of codon for Met, and six kinds of codon for Leu) are known. Accordingly, the nucleotide sequence of DNA can be changed in order to encode the polypeptide having the same amino acid sequence.

Please replace the paragraph encompassing lines 20-29, page 8, with the following paragraph:

As the following step, it is necessary to examine whether or not the DNA thus obtained correctly codes for a protein including signal peptides. The examination requires:

(I) the conversion of the DNA sequence into the amino acid sequence in a possible frame,

(II) the preparation of hydrophobicity profile from the amino acid sequence conversed, followed by confirmation of the existence of a highly hydrophobic region just after the translation initiation codon (ATG)(membrane proteins have highly hydrophobic signal peptides on their N-termini), and then

Please replace the paragraph encompassing lines 23-27, page 10, with the following paragraph:

The polypeptide of the present invention is produced from an endothelial cell line of umbilical cord vein and may possess biological activities relating to adhesion of platelet, kinds of leukocytes (e.g. lymphocyte, neutrophil, eosinophil leukocyte, basocyte and monocyte) and

Please delete line 27, page 11.

Please renumber pages 21-26 as pages 1-6, reflecting current Patent Office practice to number pages of a Sequence Listing separately.

Please delete page 27 in its entirety, and renumber pages 28 and 29 as pages 21 and 22.

IN THE CLAIMS:

Please cancel claims 1, 2 and 8-10 without prejudice or disclaimer.

Please enter the following amended claims:

3. (Amended) An isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 1.

4. (Amended) The polynucleotide according to claim 3, comprising a DNA sequence of SEQ ID NO: 2.

5. (Amended) The polynucleotide according to claim 3, comprising a DNA sequence of SEQ ID NO: 3.

6. (Amended) A replication and expression vector comprising the isolated polynucleotide according to claim 3.

7. (Amended) Host cells transformed or transfected with a replication and expression vector according to claim 6.

Please add the following new claims:

11. A method of producing a polypeptide comprising:

(a) culturing a host cell which has been transformed or transfected with a replication and expression vector, wherein the vector comprises an isolated polynucleotide which encodes a polypeptide comprising an amino acid sequence of SEQ ID NO: 1, under conditions suitable to express the polypeptide; and

(b) recovering the polypeptide.

12. A replication and expression vector comprising the isolated polynucleotide according to claim 4.

13. Host cells transformed or transfected with a replication and expression vector according to claim 12.

14. A replication and expression vector comprising the isolated polynucleotide according to claim 5.

15. Host cells transformed or transfected with a replication and expression vector according to claim 14.

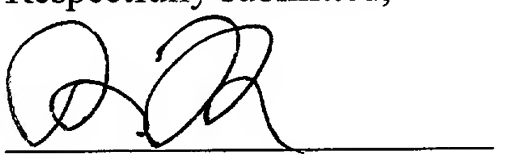
REMARKS

The amendments to the specification at lines 1-9, page 4, are made to correct an obvious error. SEQ ID NO: 1, in the Sequence Listing, clearly shows that the amino acid residues in the first position of the polypeptide of SEQ ID NO: 1 is methionine. Similarly, the amino acid residue at position 24 of the polypeptide is shown to be serine.

The additional amendments to the specification and claims are made to more clearly state that which Applicants regard as their invention.

Accordingly, no new matter has been added, and entry and consideration of this Amendment is respectfully requested.

Respectfully submitted,



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Date: February 25, 2002

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE TITLE:

The title has been amended as follows:

A ~~NOVEL~~ POLYPEPTIDE AND DNAs ENCODING IT

IN THE SPECIFICATION:

The specification has been amended by inserting before the "Field of the Invention" the following sentence:

This is a continuation of Application No. 09/246,355 filed February 8, 1999, which is a continuation application of U.S. Application No. 08/852,811 filed May 7, 1997, which is a continuation application of U.S. Application No. 08/439,457 filed May 11, 1995; the above noted prior applications are all hereby incorporated by reference.

The section of the specification entitled "Field of the Invention" (encompassing lines 1-6) has been inserted before the section entitled "Related Arts.

The paragraph encompassing lines 9-17, page 1, has been amended as follows:

Related Art~~Arts~~

Vascular organization consists of endothelial cells, smooth muscle cells and fibroblasts. Especially, endothelial cells have the following serious functions;

1) regulation of vasotonia,

2) regulation of antithrombus and

3) response to disturbance factors of inflammation or immunity. It is thought that disturbance of the endothelial cells or anomaly of functional modulation is one cause ~~of causes~~ of arteriosclerosis or inflammatory diseases.

The paragraph encompassing lines 11-16, page 2, has been amended as follows:

Summary ~~Purpose~~ of the Invention

As described previously, it is clear ~~cleared~~ that factors concerning regulation of vasotonia, response to disturbance factors of inflammation or immunity and regulation of antithrombus are produced from vascular endothelial cells. These facts suggest that the other factors which have the same functions are produced from endothelial cells.

The paragraph encompassing lines 17-19, page 2, has been amended as follows:

The present inventors have directed their attention to this point and energetic research has been carried out in order to find novel factors which an ~~a~~ endothelial cell generates.

The paragraph encompassing lines 1-2, page 3, has been amended as follows:

factor, which makes it ~~and it makes~~ difficult to isolate and to purify the factor and to confirm its biological activity.

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The paragraph encompassing lines 19-24, page 3, has been amended as follows:

Detailed Description ~~Constitution~~ of the Invention

The present invention is related to:

(1) a polypeptide having an amino acid sequence shown in SEQ ID No. 1,

(2) a DNA encoding the polypeptide described above (1),

(3) a DNA having a nucleotide sequence shown in SEQ ID No. 2, and

(4) a DNA having a nucleotide sequence shown in SEQ ID No. 3.

The paragraph encompassing lines 1-9, page 4, has been amended as follows:

polypeptide of the present invention has a signal peptide region which is located from the methionine (Met) ~~serine (Ser)~~ at the 1st position to the serine (Ser) ~~glycine (Gln)~~ at the 24th position in the amino acid sequence shown in SEQ ID NO. 1. The essential sequence for biological activity is the amino acid sequence where the signal peptide is removed from the amino acid sequence. The signal peptide is not required for biological activity. On the other hand, the peptide of the present invention was confirmed transmembrane domain which is located from amino acid at the 119th position to amino acid at the 146th position in the amino acid sequence shown by SEQ ID No. 1 (see Figure 3).

The paragraph encompassing lines 13-20, page 5, has been amended as follows:

A further embodiment of the invention provides replication and expression vectors comprising DNA according to the invention. The vectors may be, for example, plasmid, virus or phage vectors provided with an origin of replication, optionally a promoter for the expression of the ~~said~~ DNA and optionally a regulator of the promoter. The vector may contain one or more selectable marker genes, for example an ~~a~~ anpicillin resistance gene. The vector may be used in vitro, for example of the production of RNA corresponding to the DNA, or used to transfect or transform a host cell.

The paragraph encompassing lines 3-7, page 6, has been amended as follows:

DNA according to the invention may also be inserted into the vectors described above in an antisense orientation in order to provide ~~proved~~ for the production of antisense RNA.

Antisense RNA may also be produced by synthetic means. Such antisense RNA may be used in a method of controlling the levels of a polypeptide of the invention in a cell.

The paragraph encompassing lines 1-5, page 7, has been amended as follows:

As is well-known ~~known well~~, there are one to six kinds of codon as that encoding one amino acid (for example, one kind of codon for Met, and six kinds of codon for Leu) are known. Accordingly, the nucleotide sequence of DNA can be changed in order to encode the polypeptide having the same amino acid sequence.

The paragraph encompassing lines 20-29, page 8, has been amended as follows:

As the following step, it is necessary to examine whether or not the DNA thus obtained correctly codes for ~~codes right~~ a protein including signal peptides. The examination requires:

(I) the conversion of the DNA sequence into the amino acid sequence in a possible frame,

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The paragraph encompassing lines 23-27, page 10, has been amended as follows:

~~Effects of the Invention~~

The polypeptide of the present invention is produced from an endothelial cell line of umbilical cord vein and may possess biological activities relating to adhesion of platelet, kinds of leukocytes (e.g. lymphocyte, neutrophil, eosinophil leukocyte, basocyte and monocyte) and

Line 27, page 11, has been amended as follows:

~~Application to Pharmaceuticals~~

Pages 21-26 have been renumber as pages 1-6 to reflect current Patent Office practice to number pages of a Sequence Listing separately.

Page 27 has been deleted in its entirety, and pages 28 and 29 have been renumbered as pages 21 and 22.

IN THE CLAIMS:

Claims 1, 2, and 8-10 are canceled.

The claims are amended as follows:

3. (Amended) An isolated polynucleotide ~~DNA~~ encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 ~~according to claim 1~~.

4. (Amended) The polynucleotide ~~DNA~~ according to claim 3, comprising a DNA ~~having the nucleotide~~ sequence of ~~shown in~~ SEQ ID NO: ~~No. 2 or a fragment thereof capable of selectively hybridizing to SEQ ID No. 2~~.

5. (Amended) The polynucleotide ~~DNA~~ according to claim 3, comprising a DNA ~~having the nucleotide~~ sequence of ~~shown in~~ SEQ ID NO: ~~No. 3 or a fragment thereof capable of selectively hybridizing to SEQ ID No. 3~~.

6. (Amended) A replication and expression vector comprising the isolated polynucleotide ~~DNA~~ according to claim 3 ~~any one of claims 3 to 5~~.

7. (Amended) Host cells transformed or transfected with a replication and expression vector according to claim 6.

Claims 11-15 are added as new claims.